

Acne: Medical Management What's New?

Andrea L. Zaenglein, MD
Professor of Dermatology and Pediatrics
Penn State/ Hershey Medical Center
Hershey, PA

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Conflicts of Interest

- AAD Acne Guidelines – Work group member
- American Acne Rosacea Society – Past President
- AAD iPLEDGE Work Group- Member
- *Pediatric Dermatology* – Editor-in-Chief
- Ortho Dermatologics – Advisory Board Member
- Dwight & Church - Consultant

Hot Topics: Acne

- New  Acne Guidelines
- Isotretinoin/  **iPLEDGE**[®]
Committed to Pregnancy Prevention
- Acne Vaccine
- Acne Fighting Sponge



AAD 2024 Acne Guidelines

FROM THE ACADEMY

Guidelines of care for the management of acne vulgaris

Rachel V. Reynolds, MD (Co-Chair),^a Howa Yeung, MD, MSc,^b Carol E. Cheng, MD,^c
Fran Cook-Bolden, MD,^d Seemal R. Desai, MD,^{e,f} Kelly M. Druby, BSN,^g Esther E. Freeman, MD, PhD,^h
Jonette E. Keri, MD, PhD,^{i,j} Linda F. Stein Gold, MD,^k Jerry K. L. Tan, MD,^{l,m} Megha M. Tollefson, MD,ⁿ
Jonathan S. Weiss, MD,^{b,o} Peggy A. Wu, MD, MPH,^p Andrea L. Zaenglein, MD,^q
Jung Min Han, PharmD, MS,^r and John S. Barbicri, MD, MBA (Co-Chair)^s

- Reinforces antimicrobial stewardship
- Highlights the role of hormonal therapies
- New GRADE methodology
- Incorporates cost/ patient values into recommendations



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- Risk Evaluation and Mitigation Strategy (REMS)
- iPLEDGE was the first, initiated in 2006 and approved as an official REMS program in 2010
- Isotretinoin Products Manufacturers Group (IPMG)
 - Shared REMS
 - Members not made public
 - Only contact through generic email ipledge@REMS-pmo.com
 - ? Dermatologist in group

AAD iPLEDGE Work Group



1. Decrease attestation for patients who cannot get pregnant
 2. Remove 19-day lockout
 3. Greater transparency/ stakeholder involvement
- Others: improved website interface, increase emergency contraception education, immediate start for LARC, remove CLIA requirement and keep allowing home pregnancy tests

FDA Meeting



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- Combined Meeting of the Drug Safety and Risk Management Advisory Committee and Dermatologic and Ophthalmic Drugs Advisory Committee
 - March 28-29, 2023
- FDA, IPMG, DSaRM, DODAC, Stakeholders (AAD, AARS, SPD), public comment

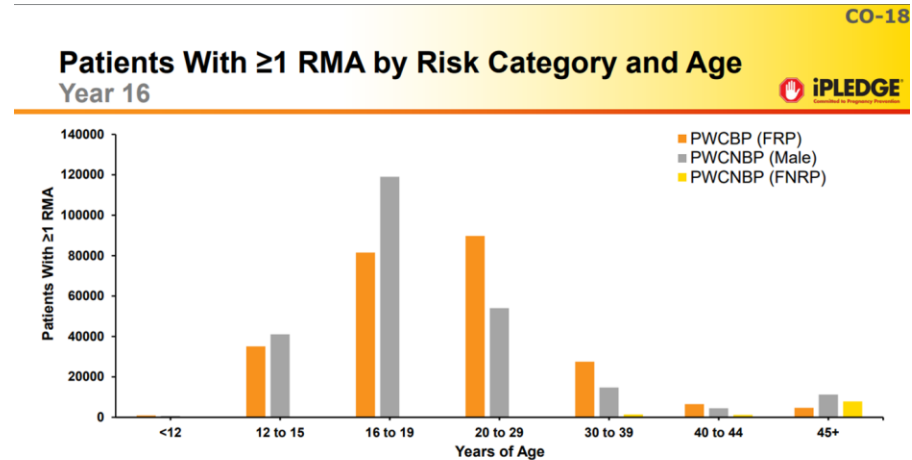
<https://www.fda.gov/advisory-committees/advisory-committee-calendar/march-28-29-2023-joint-meeting-drug-safety-and-risk-management-advisory-committee-and-dermatologic#event-materials>

Day 2 https://www.youtube.com/watch?v=_Vfks-Hczyk



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- Years 1-16: over **2M** patients enrolled
- Year 16: **297,745** patients enrolled
 - PWCBP(Female) 151,735
 - FNRP 5872
 - PWCNBP (Male) 140,138



Note: Prior to October 8, 2021, Patients Who Cannot Become Pregnant were categorized as either Females of Non-Reproductive Potential or Males.
FNRP = Females of Non-Reproductive Potential; PWCBP = Patients Who Can Become Pregnant; PWCNBP = Patients Who Cannot Become Pregnant; RMA = Risk Management Authorization.

Pregnancy on isotretinoin

Impact of Risk Management Programs

U.S. < 1 per 1000

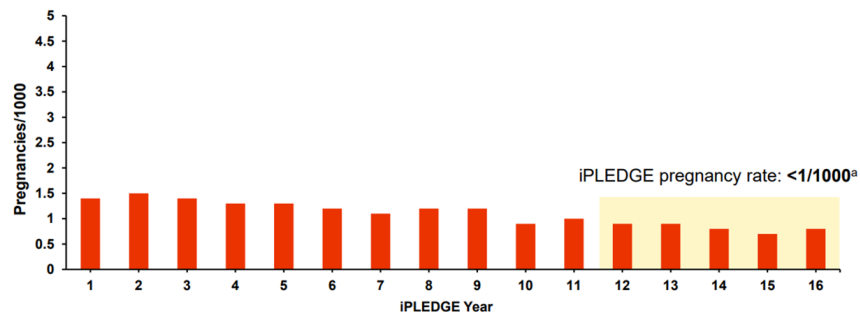
Denmark, Italy, Netherlands, Spain 0.2–1.0 per 1,000*

Canada 3.1 (to 6.2) per 1000

NZ 7.3 per 1000

iPLEDGE Pregnancy Rate Has Been Consistently Low Years 1-16

CO-22



* PWCBP enrolled in iPLEDGE with at least one RMA.

*not registry data

Durán CE, et al. Impact of the 2018 revised Pregnancy Prevention Programme by the European Medicines Agency on the use of oral retinoids in females of childbearing age in Denmark, Italy, Netherlands, and Spain: an interrupted time series analysis. *Front Pharmacol.* 2023;14:1207976.

Henry D, et al. Occurrence of pregnancy and pregnancy outcomes during isotretinoin therapy. *CMAJ.* 2016;188(10):723-730

Kovitwanichkanont T, Driscoll T. A comparative review of the isotretinoin pregnancy risk management programs across four continents. *Int J Dermatol.* 2018;57(9):1035-1046.



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Primary / Secondary Contraception Methods	Year 16 N (%)		
	Patients ^b	Pregnant Patients ^c	Rate of Pregnancy ^d
Abstinence / n/a	115028 (47.0)	47 (25.5)	0.4
Birth control Pill (combination type) / Male Latex condoms	76335 (31.2)	107 (58.2)	1.4
Hormonal IUD / Male Latex condoms	21020 (8.6)	7 (3.8)	0.3
Hormonal Implants Under-the-skin / Male Latex condoms	7203 (2.9)	3 (1.6)	0.4
Non-Hormonal IUD / Male Latex condoms	6888 (2.8)	4 (2.2)	0.6
Other ^a	18327 (7.5)	16 (8.7)	0.9
Total Individuals^b	244801 (100)	184 (100)	-

N = 184

Elective abortion	62
Spontaneous abortion	15
Missed abortion	1
Ectopic pregnancy	5
Live birth	0
Ongoing	53
Lost to follow up	43

Latest Updates (11/30/2023)

1. Pregnancy tests no longer required to be in CLIA-certified laboratory*
2. Pre-treatment pregnancy testing must be in a medical setting (eg, prescriber's office, laboratory)*
3. Pregnancy testing during and after isotretinoin treatment may be done with home pregnancy tests*
4. Prescribers who rely on the patient to perform a pregnancy test at home need to take steps to minimize falsified results*
5. Remove the "19-day lockout" for patients if they do not obtain isotretinoin within the first 7-day prescription window
6. Revise the requirement for prescribers to document patient counseling in patients who cannot become pregnant from monthly to only at enrollment

*In effect since November 30, 2023!

<https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/iplodge-risk-evaluation-and-mitigation-strategy-rem>

Home Pregnancy Test Best Practice

- Patient writes name and date on test
- Provider documents confirmation of result and visualization of the test



Latest Updates (11/30/2023)

- 
1. Pregnancy tests no longer required for laboratory
 2. Pre-treatment pregnancy testing (eg, prescriber's office, lab)
 3. Pregnancy testing during treatment may be done with home pregnancy tests
 4. Prescribers who require pregnancy test at home need to take
 5. Remove the "19-day" window to obtain isotretinoin within
 6. Revise the requirement for patient counseling in patients who cannot become pregnant from monthly to only at enrollment

Emergency Contraception

- WHO recommends provision of EC to all at risk of unintended pregnancy
- 37% (21/57) peds derms indicated they were at least somewhat confident in their understanding of EC
- 7% (4/57) peds derms agreed/strongly agreed that they provided EC counseling to patients at initial visit and 3.5% (2/57) at follow-up visits
- 34% US resident comfortable counseling on EC

<https://www.who.int/news-room/fact-sheets/detail/emergency-contraception>

Smiley CE, Butt M, Zaenglein AL. Emergency contraception in the iPLEDGE program: A cross-sectional survey of pediatric dermatology provider understanding and practice. *Pediatr Dermatol.* 2022;39(5):727-730.

The iPLEDGE REMS



Guide For Patients Who Can Get Pregnant

The Importance of Avoiding Pregnancy on Isotretinoin

One of the most common reasons that patients get pregnant is that they do not avoid sexual contact (penis-vaginal) with a partner who could get them pregnant when they plan to be abstinent.

“...you must tell the doctor/prescriber who prescribes your isotretinoin before you engage in sexual contact (penis-vaginal) with a partner who could get you pregnant.”



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**Patient Enrollment Form for Patients who
can get Pregnant:**

I have read and understand the materials my doctor has provided to me, including the *Guide for Patients who Can Get Pregnant* and the *Fact Sheet on the iPLEDGE REMS*. I have received information on emergency birth control.
Initial: _____

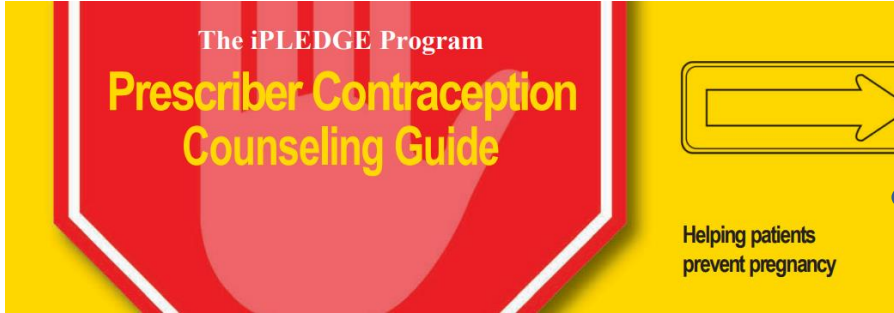


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Emergency Contraception

The patient should also realize that emergency contraception should not be used on a regular basis as a replacement for the other contraceptive forms selected.

Emergency Contraception

- Oral levonorgestrel (Plan B)
 - Take within 72 hours of unprotected intercourse/ failed contraception
 - Will not affect existing pregnancy
 - OTC \$49.99 - \$10.25 with GoodRx
- Oral ulipristal acetate (ella)
 - > 165 lbs to < 195 lbs
 - Need prescription (often covered by insurance)
 - Take within 5 days of intercourse
- Copper/hormonal IUD
 - 99.9% if inserted within 5 days of intercourse



Isotretinoin and Sexual Dysfunction

- Since 2017, Health Canada, the European Medicines Agency and many other countries have recommended that a warning for erectile dysfunction be included in isotretinoin labeling.



Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration



Government
of Canada Gouvernement
du Canada



Medicines & Healthcare products
Regulatory Agency



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Available Data: Worldwide

- RxISK.org
 - Global adverse event self-reporting website
 - Since 2012
- 300 cases of enduring sexual dysfunction from 37 countries
- 14 different drugs SSRI, 5 α -reductase inhibitors and isotretinoin

Drug	Male	Female	Total (%)
Isotretinoin	49	5	54 (18.0)
Escitalopram	30	12	42 (14.0)
Citalopram	29	12	41 (13.7)
Paroxetine	36	4	40 (13.3)
Sertraline	22	10	32 (10.7)
Fluoxetine	24	7	31 (10.3)
Finasteride	24	0	24 (8.0)
Venlafaxine	16	3	19 (6.3)
Duloxetine	8	2	10 (3.3)
Fluvoxamine	2	0	2 (0.7)
Vortioxetine	2	0	2 (0.7)
Clomipramine	1	0	1 (0.3)
Desvenlafaxine	1	0	1 (0.3)
Dutasteride	1	0	1 (0.3)

Healy D, Le Noury J, Mangin D. Enduring sexual dysfunction after treatment with antidepressants, 5 α -reductase inhibitors and isotretinoin: 300 cases. *Int J Risk Saf Med.* 2018;29(3-4):125-134. doi: 10.3233/JRS-180744.

Hogan C, Le Noury J, Healy D, Mangin D. One hundred and twenty cases of enduring sexual dysfunction following treatment. *Int J Risk Saf Med.* 2014;26(2):109-16. doi: 10.3233/JRS-140617.

Available Data: US

- FDA Pharmacovigilance National Database
- 181 reports of ED with isotretinoin
 - PRR of 1.24 (1.03–1.45). T
- “However, the quality of evidence is extremely limited, and mechanisms do not appear to be well-described in the literature. It is possible that acne is related to depression, which is a known risk factor for ED.”

Medications Most Commonly Associated With Erectile Dysfunction

Table 1. Medical specialty and PRR of medications with the highest frequency of ED adverse event reports.

Medication	Medical Specialty	Class	Mechanism of Action	Number of ED Reports	PRR
Finasteride	Urology	BPH	5-ARI	2,650	110.03 (103.14-117.39)
Dutasteride	Urology	BPH	5-ARI	173	9.40 (7.83-11.05)
Amlodipine	Cardiology	Antihypertensive	Calcium channel blocker	253	1.99 (1.71-2.30)
Paliperidone	Neuropsychiatry	Antipsychotic	Dopamine and serotonin receptor antagonism	190	1.75 (1.46-2.05)
Citalopram	Neuropsychiatry	Antidepressant	SSRI	236	1.59 (1.36-1.84)
Sertraline	Neuropsychiatry	Antidepressant	SSRI	318	1.30 (1.13-1.48)
Isotretinoin	Dermatology	Acne	Retinoid	181	1.24 (1.03-1.45)
Escitalopram	Neuropsychiatry	Antidepressant	SSRI	141	1.22 (0.99-1.46)
Quetiapine	Neuropsychiatry	Antipsychotic	Dopamine and serotonin receptor antagonism	211	1.01 (0.85-1.17)
Simvastatin	Cardiology	Antihyperlipidemic	HMG-CoA reductase inhibitors	152	0.99 (0.82-1.18)
Olanzapine	Neuropsychiatry	Antipsychotic	Serotonin, dopamine, histamine, and α -adrenergic receptor antagonism	169	0.93 (0.77-1.10)
Fluoxetine	Neuropsychiatry	SSRI	Inhibits re-uptake of serotonin	123	0.93 (0.74-1.12)

Available Data: US

- TriNetX database
- August 16, 2003 - August 16, 2023
- Male acne patients 14–40 years
- 3 Groups compared (13,600 each):
 1. Acne managed with isotretinoin with no prior tetracycline exposure
 2. Acne managed with tetracycline
 3. Acne managed without systemic medications
- Isotretinoin vs Tetracycline
- No significant differences in risk of:
 - Erectile dysfunction
(aRR [95% CI]) = (1.0 [0.55–1.8])
 - Sexual dysfunction
(0.74 [0.39–1.38])
 - Decreased libido
(1.0 [0.42–2.4])
 - Phosphodiesterase 5 Inhibitors use
(1.7 [0.88–3.2])
- Similar results isotretinoin vs no systemic treatment

Pathogenesis: *C. acnes*

- Whole genome sequencing shows that isotretinoin selectively increases *C. acnes* strain β -diversity
- CAMP2, a secreted virulence factor from *C. acnes*, can induce inflammatory responses
- The targeting of CAMP2 in a vaccination approach could inhibit *C. acnes* pathogenicity as evidenced by the anti-inflammatory properties of antibodies to this virulence factor
- Antibodies to CAMP decrease the inflammatory response to *C. acnes* in mice and ex vivo in human acne explants.
 - Decreased MIP-2 (a murine neutrophil chemoattractant) in mice
 - Decreased IL-8 and IL-1 β in a human explant model



Vaccine Trial



- A Phase I, Multi-center, Double-blind, Randomized, Dose Escalating, Parallel Group, Placebo-controlled Safety, Tolerability and Immunogenicity Study of ORI-A-ce001 for the Treatment of Facial Acne Vulgaris
- mRNA vaccine based on recombinant proteins

Pathogenesis: *C. acnes*

- Two variants of hyaluronidase (HylA, HylB) are produced by *C. acnes*
- HylA is associated with acne (pro-inflammatory)
- HylB is associated with healthy skin (anti-inflammatory)
- Mouse model: immunized against HylA improved acne disease score and inflammation



Spongilla lacustris

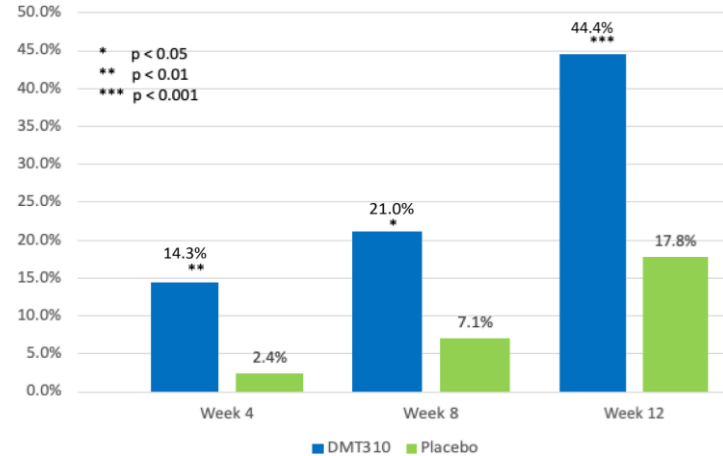
- Freshwater sponge
- 70% inorganic silica
- Organic spongin and α -chitin
 - Antiinflammatory in keratinocytes
 - Antimicrobial against *C. acnes*
 - Decrease lipogenesis in sebocytes
- Spicules penetrate stratum corneum delivering the organic compounds



DMT310

- Phase 2 RCT
- 181 pts, 12 years and older, moderate-severe acne
- DMT310 in 3% H₂O₂ vs. placebo (3% H₂O₂)
- Applied once weekly left on 10-15 minutes

IgA Success



Noninflammatory: mean lesion count -18.3 vs -12.4,
% change baseline -58% vs -36%

Inflammatory: mean lesion count -15.6 vs -10.5,
% change baseline -62% vs -42%

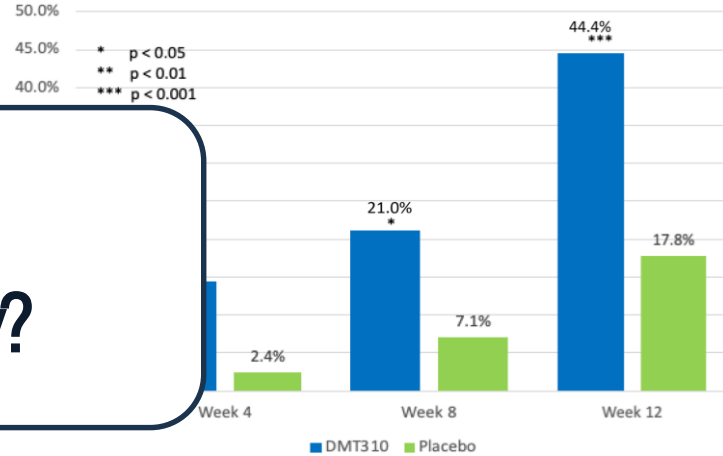
DMT310

- Phase 2 RCT
- 181 pts, 12 years and older, moderate to severe acne



Is Your Acne Spongeworthy?

IgA Success



and once weekly left
5 minutes

Noninflammatory: mean lesion count -18.3 vs -12.4,
% change baseline -58% vs -36%

Inflammatory: mean lesion count -15.6 vs -10.5,
% change baseline -62% vs -42%

Conclusions

- Meaningful changes to iPLEDGE
- Counsel and prescribe emergency contraception for patients on isotretinoin
- New basic science data is guiding new therapy
- ? Vaccines targeting CAMP and HyLA
- Natural treatments: *Spongilla lacustris*

